PROGNOSTIC VALUE OF ADMISSION GLUCOSE AND GLYCOSYLATED HAEMOGLOBIN LEVELS IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION

Dissertation submitted for

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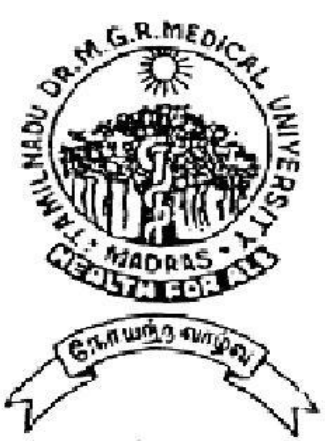
General Medicine



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CERTIFICATE

This is to certify that this dissertation titled **"PROGNOSTIC VALUE OF ADMISSION GLUCOSE AND GLYCOSYLATED HAEMOGLOBIN LEVELS IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION"** submitted by **DR. BEATRICE ANNE.M** to the faculty of General Medicine, The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree **Branch I (General Medicine)** is a bonafide research work carried out by her under our direct supervision and guidance.

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I, **Dr. BEATRICE ANNE.M**, solemnly declare that the dissertation titled **'PROGNOSTIC VALUE OF ADMISSION GLUCOSE AND GLYCOSYLATED HAEMOGLOBIN LEVELS IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION'** has been prepared by me.

This is submitted to the Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree Branch I (General Medicine).

Place: Madurai

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CONTENTS

PROGNOSTIC VALUE OF ADMISSION GLUCOSE AND GLYCOSYLATED HAEMOGLOBIN LEVELS IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION

ABSTRACT

BACKGROUND: Coronary heart disease is common in people with diabetes mellitus. Diabetes is associated with a poor prognosis in patients with an acute coronary syndrome (ACS), either with or without ST-elevation (STEMI/non-STEMI). However, more acute glycometabolic disturbances may also have a negative impact on outcome. Elevated glucose levels on admission are associated with increased mortality after ACS, irrespective of diabetic status. Whether HbA_{1c} levels have the same prognostic significance as glucose levels in an emergency setting is unknown.

AIM: To investigate the prognostic value of admission glucose and glycosylated hemoglobin levels in acute ST elevation myocardial infarction and to assess the importance of long term blood glucose control as reflected by HbA1c in predicting outcome after acute ST elevation myocardial infarction.

METHODS: This was a prospective observational study conducted on 80 patients admitted to the Cardiology ICCU ward at Government Rajaji Hospital, Madurai with acute ST elevation myocardial infarction, irrespective of their previous diabetic status. We measured blood glucose and Hba1c at admission in these patients. The 80 patients included in this study were further stratified into five groups, based on previous history of diabetes, blood glucose levels at admission and HbA1c levels. Group 1(uncontrolled diabetes) included patients with previous history of diabetes with HbA1c > 6.5 %.Group 2(controlled diabetes) included those with previous history of diabetes with HbA1c ≤ 6.5 %.Group 3 (stress hyperglycemia) was patients with no previous history of diabetes, random blood glucose at admission ≥ 200 mg/dl and HbA1c < 6.5 %.Group 4 (undiagnosed diabetes)included those with no previous history of diabetes, random blood glucose ≥ 200 mg/dl and HbA1c ≥ 6.5%.Group 5(nondiabetic) included those with no previous history of diabetes, random blood glucose < 200 mg/dl and HbA1c < 6.5

%.These patients were followed up during the hospital stay and complication rates were assessed.

RESULTS : There were 27 subjects under group 1 (uncontrolled diabetes) of which 70.4 % had complications during hospital stay and 66.7 % had a left ventricular ejection fraction(LVEF) ≤ 40 %.Among the 5 patients in group 2 (controlled diabetes),only 1 developed complication during hospital stay and all had an LVEF > 40 %.In group 3 (stress hyperglycemia),both patients developed complications and had an LVEF ≤ 40 %.There were 9 subjects in group 4 (undiagnosed diabetes),out of which 66.7 % developed complications and all had an LVEF ≤ 40 %.Group 5 included 37 patients, out of which only 8.1 % developed complications and only 13.5 % had an LVEF ≤ 40 %. Moreover, there was a significant negative correlation between HbA1c levels and left ventricular ejection fraction. There was also a significant negative correlation between admission blood glucose levels and left ventricular ejection fraction.

DISCUSSION: Our results suggest that both acute and chronic hyperglycemia are independent predictors of adverse outcome after acute ST elevation myocardial infarction. Hence, measurement of both blood glucose as well as HbA1c enables identification of these high risk groups for aggressive management.

INTRODUCTION

The global prevalence of diabetes mellitus has been estimated to be at 170 million individuals and is rapidly increasing with projections of > 350 million by 2030.Coronary heart disease is common in people with diabetes mellitus. The presence of elevated blood glucose levels, diabetes mellitus, or both contribute to more than 3 million cardiovascular deaths worldwide each year. Diabetes is associated with a poor prognosis in patients with an acute coronary syndrome (ACS), either with or without ST-elevation (STEMI/non-STEMI). [1–3] However, more acute glycometabolic disturbances may also have a negative impact on outcome. Elevated glucose levels on admission are associated with increased mortality after ACS, irrespective of diabetic status. [4–8] Recent evidence has shown that chronic glucose dysregulation, as assessed by glycosylated hemoglobin (HbA_{1c}) levels, may also be of prognostic value with regard to future cardiovascular disease. [9,10] Whether HbA_{1c} levels have the same prognostic significance as glucose levels in an emergency setting is unknown. This study was undertaken to investigate the independent prognostic value of HbA1c levels and admission glucose in patients with acute ST elevation myocardial infarction, irrespective of their diabetic status.

CORONARY ARTERY DISEASE:

The term "Acute Coronary Syndrome" (ACS) refers to a range of acute myocardial ischemic states which include unstable angina, non ST elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI).Despite significant advances in the diagnosis and management, ACS remains a significant global problem with very high mortality and morbidity. The pathogenetic process central to the initiation of an ACS is disruption /fissuring of an atheromatous plaque and consequent exposure of core constituents such as lipid, smooth muscle, and foam cells, leading to the local generation of thrombin and deposition of fibrin. This in turn promotes platelet aggregation and adhesion and the formation of intracoronary thrombus[11]. STEMI continues to be a significant public health problem in industrialized countries and is becoming an increasingly significant problem in developing countries.[12]

DEFINITION:

A recent expert consensus document redefined acute MI as the detection of a rise and /or fall in cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit (URL), together with evidence of ischemia. Ischemia was defined as any

symptoms of ischemia (chest pain, breathlessness, syncope, confusional state, arrhythmias), electrocardiographic changes suggestive of new ischemia, development of pathologic Q waves on electrocardiogram (ECG) or imaging evidence of infarction. Included in the definition was sudden cardiac death with evidence of myocardial ischemia (new ST elevation, left bundle branch block, or coronary thrombus), biomarker elevation >3×URL for post PCI patients, or >5 ×URL for post coronary artery bypass grafting (post-CABG) patients. Documented stent thrombosis was recognized in this new definition as well. Established MI was defined as any one criterion that satisfies the following: development of new pathologic Q waves on serial ECGs, imaging evidence of MI,or pathologic findings of healed or healing MI.[13]

PATHOPHYSIOLOGY:

The pathophysiologic hallmark of ACS is that of:

1) A fissured atherosclerotic plaque with a platelet rich thrombus which is subtotally/completely occlusive, often over mild to moderately stenotic lesions along with

2) Impaired distal circulation due to micro embolisation from the plaque disruption.

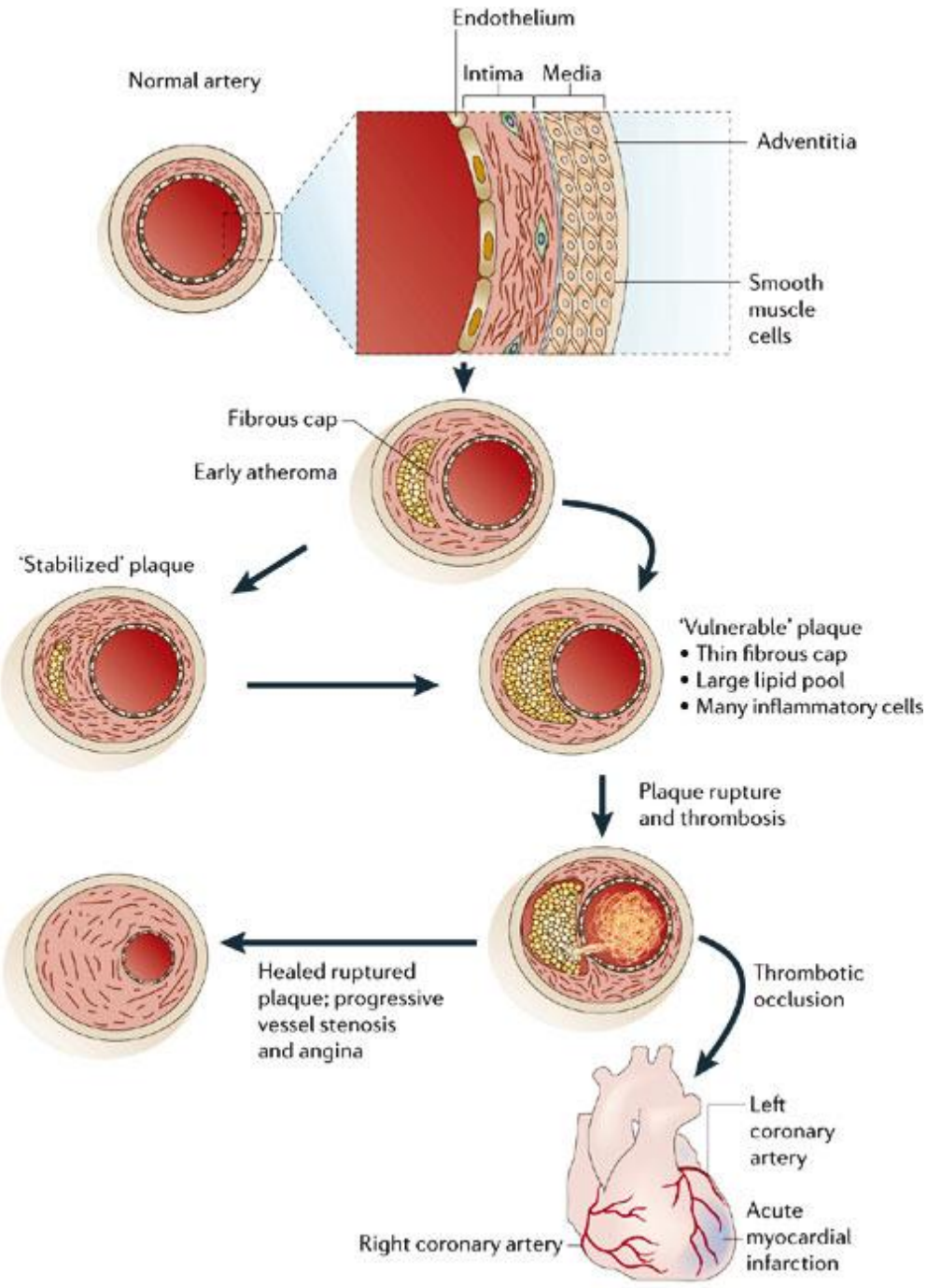
3) Other causative/perpetuating mechanisms: vasospasm.

The eventual outcome (UA / NSTEMI / STEMI / Sudden cardiac death) depends upon the anatomical location of the lesion, extent of plaque disruption and duration & type of occlusion. Coronary angiogram early in STEMI reveals complete occlusion of the culprit artery in around 90% of patients. However, in NSTE-ACS, the culprit vessel is not occluded in 60-85% of patients. In STEMI, the complete occlusion of an epicardial coronary artery occurs due to fibrin rather than platelet rich thrombus. The thrombotic mechanisms have an impact on the way these syndromes are treated, both in the coronary care & catheter laboratory setting.

VULNERABLE PLAQUE:

Basically, plaque formation in human coronary arteries could start as early as second decade. A coronary plaque consists of a lipid core surrounded by a fibrous cap. With age, a stable plaque may progress without major disruption & cause no symptoms or stable angina. The relative thickness & consistency of the lipid & the fibrous core determines the propensity of the plaque to rupture. Also, there is plenty of evidence now from studies which show that the inflammatory cascade is at the heart of the plaque rupture, responsible for initiation & sustenance of the effects which result in a subclinical or frank ACS.

PATHOPHYSIOLOGY OF ACS



Altered / reduced collagen support combined with inflammatory activity makes the plaque highly vulnerable.

The larger the lipid core & the thinner the fibrous cap, the more vulnerable is the atheroma to rupture. The basic mechanisms involved in plaque rupture are:

- Problems with collagen in the fibrous cap
- Various triggers, including mechanical stress
- Sympathetic stimulation
- Inflammation

Collagen cap problems: Interstitial collagen is the main constituent of the fibrous cap layer of the plaque & is formed by the smooth muscle cells. Three mechanisms may affect this aspect of the plaque: a) impaired collagen formation by smooth muscle cells, b) breakdown of smooth muscle cells & c) collagen breakdown by various enzymes (collagenases, matrix metalloproteinase) secreted preferentially in the vulnerable regions of the plaque. Dysfunctional collagen impairs the ability of the plaque to remain stable & with the right trigger(s), the cap of the plaque gives away, commonly at the “shoulder regions”(areas of junction between a normal segment of the artery & the atheroma).This exposes the endothelial basement membrane & the central lipid core of

the atheroma(both of which being highly thrombogenic structures)to the circulating blood components, initiating the platelet & coagulation cascade &eventually causing micro/macro thrombosis with/without symptoms/events.

In STEMI, after an initial platelet monolayer forms at the site of the disrupted plaque, various agonists (collagen, ADP, epinephrine, serotonin) promote platelet activation. After agonist stimulation of platelets, thromboxane A2 (a potent local vasoconstrictor) is released, further platelet activation occurs and potential resistance to fibrinolysis develops. In addition to the generation of thromboxane A2, activation of platelets by agonists promotes a conformational change in the glycoprotein IIb / IIIa receptor. Once converted to its functional state, this receptor develops a high affinity for amino acid sequence on soluble adhesive proteins (i.e., integrins) such as fibrinogen. Since fibrinogen is a multivalent molecule, it can bind to two different platelets simultaneously, resulting in platelet cross-linking and aggregation. The coagulation cascade is activated on exposure of tissue factor in damaged endothelial cells at the site of the disrupted plaque. Factors VII and X are activated, ultimately leading to the conversion of prothrombin to thrombin, which then converts fibrinogen to fibrin. Fluid-phase and clot-

bound thrombin participate in an auto amplification reaction leading to further activation of the coagulation cascade. The culprit coronary artery eventually becomes occluded by a thrombus containing platelet aggregates and fibrin strands.

Triggers for ACS:

Increased sympathetic stimulation is well known to cause ACS & the underlying mechanism could include rise in heart rate & the blood pressure which increase plaque “stress” & increase thrombogenicity by stimulating platelet activity. This has been thought to be the basis of increased incidence of ACS in the early morning hours due to heightened sympathetic surge. Also, in predisposed individuals, exercise or emotional stress might cause plaque rupture due to catecholaminergic surge leading to increased wall stress. Other mechanisms also include vasospasm, mechanical effects due to rapid, increased flexing of coronary arteries(at the bend points on the epicardium). Exercise may also lead to deepening of the already existing plaque fissures & cause enhanced platelet aggregation. Mechanical stress on the morphologically vulnerable plaques makes them more prone to rupture. The flow dynamics of the coronary artery determine the level of mechanical strain experienced by the coronary atheroma.Circumferential, radial &

longitudinal deformation of the plaque contribute to the processes of inflammation, erosion, destabilization, fatigue of the cap area of the plaque and eventually plaque rupture and thrombosis. The disruption in the integrity of the plaque could occur superficially or as a deep rupture.

Role of inflammation:

There is a strong association between plaque inflammation and rupture. Compared to a stable plaque, an unstable & disrupted plaque displays significantly high inflammatory activity. Secretion of inflammatory markers like interleukins & gamma interferon play a vital role in perpetuating the process. Past studies have also found increased inflammatory potential of oxidized lipoproteins in the regions of coronary atheroma. Inflammation with its cytotoxic effects degrades the collagen layer & helps to aggravate plaque vulnerability by making it more prone to disruption & eventually thrombosis.

CLINICAL FEATURES:

The cardinal symptom is the ischemic chest pain which is typically described by the patient as burning, tightness or heaviness. Patients with STEMI usually have severe chest pain with fear of dying, whereas in non-ST elevation ACS the pain is more waxing and waning, is dependent on the level of exertion, but usually lasts no longer than 20

minutes. The pain is typically located in the centre or the left lateral chest and radiates to the left shoulder, arm, neck and jaw. Pain may also be epigastric ,particularly in inferior wall MI. Perception of pain in the right side of the chest does not exclude myocardial ischemia. However, pain is not uniformly present in patients with STEMI. The proportion of painless STEMI is greater in diabetics and it increases with age. In the elderly, it may present as sudden onset breathlessness, which may progress to pulmonary edema. Other less common presentations, with or without pain, include sudden loss of consciousness, a confusional state, a sensation of profound weakness, the appearance of an arrhythmia, evidence of pulmonary embolism or merely an unexplained drop in arterial pressure.

PHYSICAL EXAMINATION:

The major purpose of the examination is to exclude non cardiac causes of chest pain, non ischemic cardiac disorders (eg.pericarditis, valvular disease), potential precipitating extra cardiac causes, pneumothorax, and to look for signs of potential hemodynamic stability and left ventricular dysfunction. The combination of substernal chest pain persisting for >30 min and diaphoresis strongly suggests STEMI. The precordium is usually quiet and the apical impulse may be difficult

to palpate. In patients with anterior wall infarction, an abnormal systolic pulsation caused by dyskinetic bulging of infarcted myocardium may develop in the periapical area within the first days of the illness and then may resolve. Other physical signs of ventricular dysfunction include fourth and third heart sounds, decreased intensity of the first heart sound and paradoxical splitting of the second sound. A transient midsystolic or late systolic apical systolic murmur due to dysfunction of the mitral valve apparatus may be present. A pericardial friction rub is heard in many patients with transmural STEMI at some time in the course of the disease. The carotid pulse is often decreased in volume, reflecting stroke volume. Temperature elevations upto 38^{o}C may be observed during the first week after STEMI.The arterial pressure is variable; in most patients with transmural infarction, systolic pressure declines by approximately 10-15mm Hg from the preinfarction state.

LABORATORY FINDINGS:

The laboratory tests can be divided into:

1) Electrocardiogram

2) Serum cardiac biomarkers

3) Cardiac imaging

4) Nonspecific indices of tissue necrosis & inflammation.

ELECTROCARDIOGRAM:

The ECG remains an important screening tool and it may also provide evidence of alternative diagnosis such as pericarditis, pulmonary embolism, or cardiomyopathy.

Definite electrocardiographic evidence of acute MI requires ST elevation of 1mm or more in two or more contiguous leads, often with reciprocal ST depression in the contra lateral leads. In leads $V_2 - V_3$, 2 mm of ST elevation in men and 1.5mm in women is required for accurate diagnosis.

New LBBB in the setting of symptoms of acute MI may indicate a large, anterior wall acute MI involving the proximal left anterior descending coronary artery and should be managed as acute MI.Right bundle branch block complicates interpretation of ST elevation in leads V_1-V_3.The diagnosis of anterior acute MI is possible when the normal secondary T wave changes in a patient with RBBB in leads V_1-V_4 are replaced with T waves of concordant polarity with the QRS(i.e. pseudonormalisation).

BIOCHEMICAL MARKERS:

MARKER	ADVANTAGES	DISADVANTAGES
CK - MB	Rapid Cost effective Detected early in infarctions	Loss of specificity with skeletal muscle damage Detection after 6 hours of myocardial necrosis
Myoglobin	Highly sensitive Early detection of MI within 2 hours Detects reperfusion Most useful in ruling out MI	Low specificity with skeletal muscle damage Rapid return to normal
Troponins	Powerful tool for risk stratification Greater sensitivity and specificity than CK – MB Detects recent MI upto 2 weeks Helpful to determine therapy Detection of reperfusion	Low sensitivity in MI of less than 6 hours Require repeat measures at 8 -12 hours if first result is negative Less able to detect late, minor MIs

	SPECIFICITY	SENSITIVITY	FIRST RISE AFTER MI	PEAK AFTER MI	RETURN TO NORMAL
CKMB	++	+	4h	24h	72h
MYOGLOBIN	+	+	2h	6-8h	24h
TROPONIN T	+++	+++	4h	24-48h	5-21days
TROPONIN I	+++	+++	3-4 h	24-36h	5-14days

CARDIAC IMAGING:

ECHOCARDIOGRAPHY: Left ventricular systolic function is an important prognostic variable in patients with ACS and can be easily and accurately be assessed by echocardiography. Regional wall motion abnormalities occur within seconds after coronary occlusion well before necrosis. However, these are not specific for acute events and maybe the result of old infarctions. Transient localized hypokinesia or akinesia in segments of the left ventricle may be detected during ischemia, with normal wall motion on resolution of ischemia. The absence of wall motion abnormalities excludes major myocardial infarction.

CORONARY ANGIOGRAPHY:

This is the gold standard to prove or exclude coronary artery disease. The extent and location of lesions is useful for risk assessment and decision making concerning revascularization by means of angioplasty or surgery. The culprit lesions that are responsible for the clinical symptoms, frequently show filling defects, indicating intracoronary thrombus formation.

MYOCARDIAL PERFUSION SCINTIGRAPHY:

A normal resting technetium 99 myocardial perfusion scintigram effectively excludes major myocardial infarction. An abnormal acute scintigram is not diagnostic of acute infarction unless it is known to be previously normal, but it does indicate the presence of coronary artery disease and the need for further evaluation.

CARDIAC MAGNETIC RESONANCE IMAGING:

The multimodality characteristic of cardiac MRI provides a comprehensive examination, combining regional contractile function, myocardial perfusion and viability. In addition, it can also rule out other potential reasons for the chest pain.

CT ANGIOGRAPHY:

It has a high negative predictive value meaning that if it is normal then there is a high likelihood that the patient is not having coronary heart disease but if CT angiography is showing stenosis in the coronary arteries that it is quite possible that it may be a false positive result.Hence, this test is useful for evaluating patients with a low probability of CAD.

RISK STRATIFICATION:

Five simple baseline parameters have been reported to account for more than 90% of the prognostic information for 30 day mortality. These are age, systolic blood pressure, Killip classification, heart rate, and location of MI.

30-DAY MORTALITY BASED ON HEMODYNAMIC (KILLIP) CLASS:

KILLIP CLASS	CHARACTERISTICS	MORTALITY (%)
I	No evidence of CHF	5.1
II	Rales,↑JVP or S_3	13.6
III	Pulmonary edema	32.2
IV	Cardiogenic shock	57.8

TREATMENT:

1) IMMEDIATE MANAGEMENT AND STABILISATION:

a) ASPIRIN: Immediate administration of aspirin is indicated for all patients with acute MI,unless there is a clear history of true aspirin allergy(not intolerance).The dose should be four, chewable 81mg tablets(for more rapid absorption)or one 325 mg nonchewable tablet. If oral administration is not possible, a rectal suppository can be given.

b) THIENOPYRIDINES: Recent data indicate that clopidogrel should be added to aspirin in STEMI patients regardless of whether they undergo primary PCI or fibrinolysis.The CLARITY-TIMI 28 trial showed pretreatment with clopidogrel to be safe and effective without increased bleeding among patients treated with fibrinolytic therapy, with many receiving subsequent PCI.The COMMIT-CCS 2 trial found a significant reduction in all-cause mortality but no difference in major bleeding. An oral loading dose of 300 mg is given followed by 75 mg daily.

c) OXYGEN: Supplemental oxygen through nasal cannula should be given to all patients with suspected MI.Administration through face mask or endotracheal tube may be necessary for patients with severe pulmonary edema or cardiogenic shock.

d) NITROGLYCERIN: It is worthwhile to give sublingual nitroglycerin (0.4 mg) to determine whether the ST segment elevation represents coronary artery spasm while arrangements for reperfusion therapy are being initiated. Nitroglycerin can be useful in the management of acute MI complicated by CHF,ongoing symptoms or hypertension.

e) REPERFUSION THERAPY: Prompt and effective reperfusion therapy is the cornerstone of treatment for acute STEMI and is the only widely applicable acute treatment to diminish infarct size and major cardiac complications. The European guidelines for the management of acute MI recommend that for patients with clear cut changes of acute infarction ,no more than 20 minutes should elapse between hospital arrival and the administration of thrombolytic therapy (or prehospital administration) or no more than 60 minutes between hospital arrival and balloon inflation for primary PCI[14].

FIBRINOLYTIC THERAPY:

AGENTS	**CHARACTERISTICS**	DOSE	TRIALS
ALTEPLASE (tPA)	Fibrin specific	15 mg bolus followed by 0.75 mg/kg(upto 50 mg) over 30 min, then 0.5mg/kg over 60 min	GUSTO I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries)
RETEPLASE	Less fibrin specific, longer half life	Double bolus(10 mg each 30 minutes apart)	GUSTO III
TENECTE PLASE (TNK)	Fibrin specific, resistant to plasminogen activator inhibitor (PAI -1)	Single bolus, 30 – 40 mg (ASSENT 1)	ASSENT 2 (Assessment of the Safety and Efficacy of a New Thrombolytic)
STREPTO KINASE	Nonfibrin specific,cheap,development of antibodies	1.5million units (7,50,000 units over 20 minutes followed by 7,50,000 units over 40 minutes)	

CONTRAINDICATIONS FOR THROMBOLYTIC THERAPY[13] :

Absolute contraindications:

- Previous hemorrhagic stroke at any time; ischemic stroke within 3 months
- Known intracranial neoplasm, structural cerebral vascular lesion or closed head injury within 3 months
- Active bleeding or bleeding diathesis (excluding menses)
- Suspected aortic dissection

Relative contraindications:

- Severe, uncontrolled hypertension at presentation (blood pressure > 180/110 mm Hg) or history of chronic severe hypertension
- History of ischemic stroke>3 months,dementia,or known intracerebral pathologic conditions not covered in contraindications
- Current use of anticoagulants, the risk increases with increasing INR
- Traumatic or prolonged (>10 min)CPR or major surgery(<3 wks)
- Noncompressible vascular punctures
- Recent (within 2-4 wks) internal bleeding
- For streptokinase : prior exposure or prior allergic reaction
- Pregnancy
- Active peptic ulcer

PRIMARY PCI:

Individual trials comparing fibrinolytic therapy with primary PCI and the meta analysis of such trials have shown that primary PCI done promptly by an experienced team is superior to fibrinolytic therapy in centres with a high volume of PCI procedures[15].Primary PCI is the preferred strategy for patients with acute ST elevation MI if, with appropriate facilities, a skilled team can provide PCI within 60 minutes of hospital arrival.

FACILITATED PCI:

Facilitated PCI may offer advantages but larger scale trials are awaited. The CAPITAL AMI trial compared fibrinolytic therapy with Tenecteplase (TNK) alone versus TNK –facilitated PCI in high risk STEMI patients. The primary composite end points of death, reinfarction, recurrent unstable angina, or stroke at 6 months were 24.4% in TNK arm and 11.5% in facilitated PCI arm.

PCI COMBINED WITH Gp IIb/IIIa inhibitors:

The combination of Gp IIb / IIIa inhibitors and primary PCI has been tested in several studies (RAPPORT, ISAR 2, CADILLAC, ADMIRAL, and ACE Trials).The pooled analysis suggests that Gp

IIb/IIIa inhibition reduces adverse outcomes (death/MI and target vessel revascularization) in primary PCI (without a lytic agent).Thus for primary PCI, addition of Gp IIb/IIIa inhibitor (abciximab) may be regarded as the modern reference standard[16].

RESCUE PCI:

Rescue PCI refers to a PCI procedure performed in patients without evidence of a response to thrombolysis (<50% ST segment resolution) and feasibility studies have demonstrated success of PCI in achieving coronary patency and flow.However,insufficient data are available to demonstrate whether there is improvement in mortality or further MI.

ROLE OF HEPARIN:

As an adjunct to tPA, heparin has been shown to improve late patency. The dose of heparin recommended by the AHA/ACC guidelines is 60U/kg bolus(maximum,4000 units) followed by 12U/kg/hr (maximum 1000 U/hr).

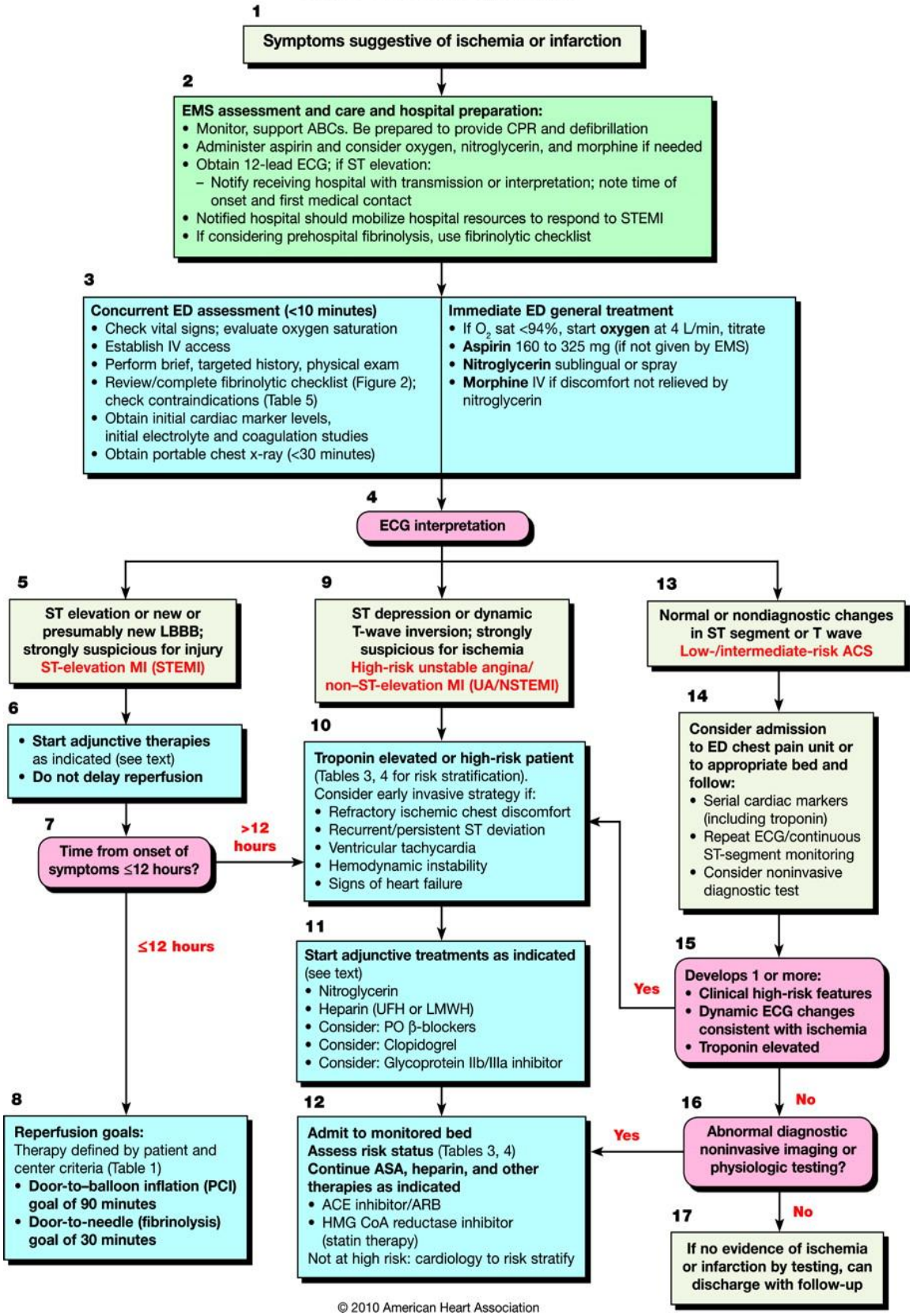
OTHER DRUGS:

Beta blockers: The TIMI IIb trial compared immediate intravenous Metoprolol (within 6 hrs of onset of chest pain)to delayed oral

metoprolol(on day 6).Early intravenous treatment was associated with significant reduction in 6 week mortality or reinfarction.ISIS 1 study also confirmed the mortality benefits of early beta-blocker therapy.

ACE inhibitors: A series of trials (SAVE, AIRE, SMILE, TRACE, GISI III, and ISIS-4) have shown both short term and long term improvement in survival after ACE inhibitor therapy. The benefits are greatest in patients with low ejection fraction, large infarctions or clinical evidence of heart failure. Because substantial amounts of the survival benefit occur on the first day, ACE inhibitor treatment should be commenced early in patients without hypotension, especially patients with large anterior wall infarctions.

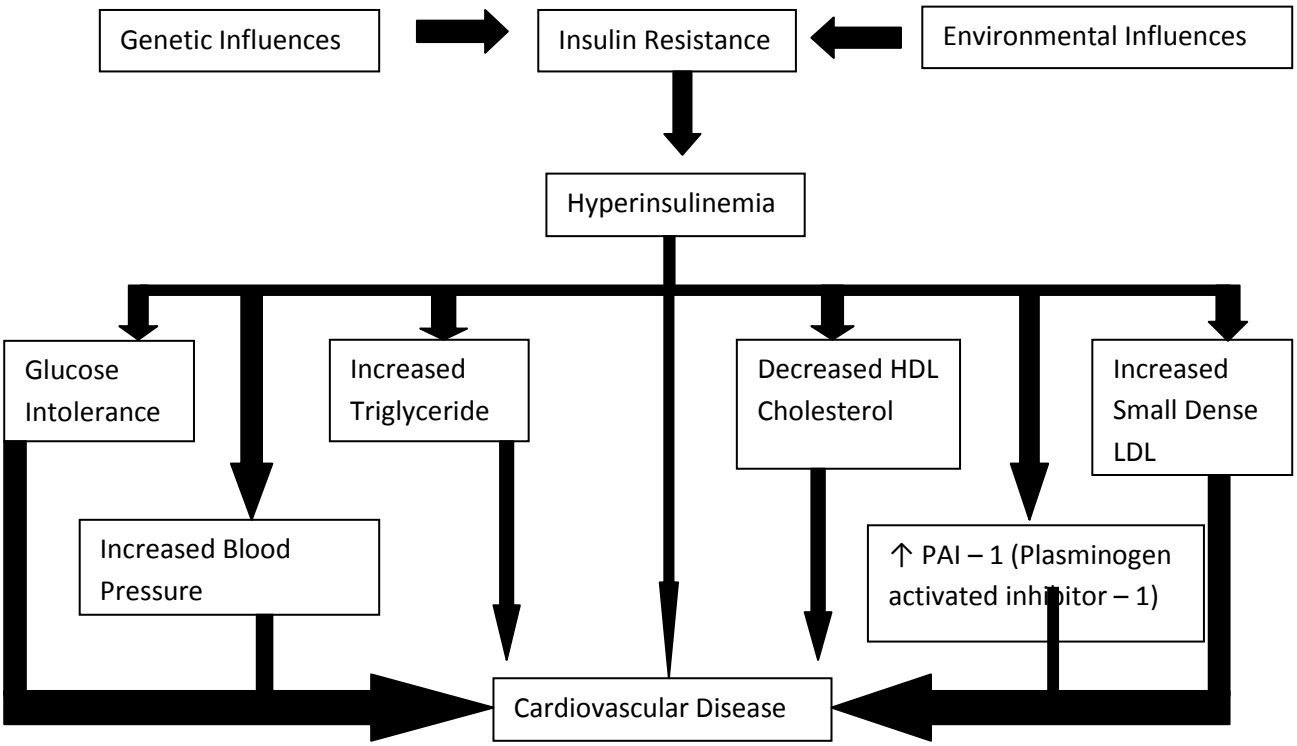
Acute Coronary Syndromes



ACUTE CORONARY SYNDROME AND DIABETES MELLITUS:

In India, there is a joint epidemic of type 2 diabetes and Coronary Artery Disease (CAD)[17].Epidemiological studies in urban and rural population performed over the last 50 yrs have clearly shown an increase in the prevalence of diabetes as well as CAD in rural and urban population. The prevalence of type2 diabetes has increased from less than 1% in rural and 1.5 in urban areas in 1960's to 6-8% in rural and 10-15% in urban population currently[18].The prevalence of CAD has increased from less than 1% in rural populations to 4-5 % presently, and in urban location from 1-2% in 1960's to 9-12% presently[18].Diabetes is now considered a cardiovascular disease equivalent by the UN National Cholesterol Education Program Guidelines. Hyperinsulinemia and insulin resistance, the hallmark abnormalities in diabetes mellitus,cause cardiovascular disease by the following mechanism.

Mechanism of Cardiovascular disease in Diabetes Mellitus



Multiple hypothesis exist to explain the occurrence of premature atherosclerosis in diabetes in India but the consensus is that it is multifactorial.Important factors include dyslipidemia, hypertension, hypercoagulability, poor glycemic control, smoking, obesity and lack of physical activity. Of these, the factors that appear mechanistically most important are

1. Hyperglycemia affecting the vessel wall
2. Diabetic dyslipidemia
3. Hyperglycemia versus dyslipidemia
4. Chronic subclinical inflammation in the vessel wall[19].

Results of basic studies in vitro, in animal models, and in patients with diabetes mellitus suggest several mechanisms by which hyperglycemia might affect atherogenesis at the level of the arterial wall[24,25].Firstly,high glucose concentrations can activate nuclear factor kB(NF-kB),which in turn can increase the expression of various genes in the endothelial cells,monocyte derived macrophages, and vascular smooth muscle cells.Secondly,advance glycation end-products(AGEs) including protein crosslinks,fluorophors and other low molecular weight residues are formed by sustained exposure of proteins and lipids to high concentrations of glucose, which can generate reactive oxygen species, ligation of AGEs to specific cell-surface receptors can regulate gene expression in vessel wall cells. Thirdly, glucose also increases oxidative stress, which has several possible harmful effects on the artery wall, e.g., auto-oxidation of glucose leads to the formation of several reactive oxygen species, such as the superoxide anion, which can promote oxidation in vitro. And fourthly, indirect observational evidence suggests that lipoprotein oxidation might be increased in patients with type 2 diabetes and is related to glycemic control. On the other hand, absence of highly specific markers in collagen, plasma, or urine from individuals with diabetes does not support a generalized increase in oxidative stress in diabetes[26,27].

CLINICAL TRIALS IN TYPE 2 DIABETES AND ACS :

1) The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was a randomized controlled study designed to determine whether normal HbA_{1c} levels would reduce the risk of cardiovascular events in middle-aged or older individuals with type 2 diabetes. About 35% of the 10,251 recruited subjects had established cardiovascular disease at study entry. The intensive arm of the study was discontinued after 3.5 years of follow-up because of more unexplained deaths in the intensive arm when compared with the control arm (22%, $P = 0.020$). Analysis of the data at time of discontinuation showed that the intensively treated group (mean HbA_{1c} 6.4%) had a 10% reduction in cardiovascular event rate compared with the standard treated group (mean HbA_{1c} 7.5%), but this difference was not statistically significant[20].

2) The Action in Diabetes and Vascular disease : Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial randomly assigned 11,140 patients with type 2 diabetes to standard or intensive glucose control. The primary outcomes were major macrovascular cardiovascular events (nonfatal myocardial infarction or stroke or death from cardiovascular causes) or microvascular events. Overall, one-third

(32%) of the subjects had established cardiovascular disease at study entry. After a median follow-up of 5 years, there was a nonsignificant reduction (6%) in major macrovascular event rate in the intensively treated group (mean HbA_{1c} 6.5%) compared with the standard therapy group (HbA_{1c} 7.3%)[21].

3) The Veteran Administration Diabetes Trial (VADT) randomly assigned 1791 patients from age 50 to 69 years with type 2 diabetes to standard or intensive glucose control. Overall, 97% of the subjects were men. The primary outcome was a composite of myocardial infarction, death from cardiovascular causes, congestive heart failure, vascular surgery, inoperable coronary artery disease, and amputation for gangrene. All the patients had optimized blood pressure and lipid levels. After a median follow-up of 5.6 years, there was no significant difference in the primary outcome in the intensively treated group (HbA_{1c} 6.9%) compared with the standard therapy (HbA_{1c} 8.4%)[22].

Thus, the ACCORD, ADVANCE, and VADT results do not provide support for the hypothesis that near-normal glucose control in patients with type 2 diabetes will reduce cardiovascular events. It is, however, important not to over-interpret the results of these three studies. The results do not exclude the possibility that cardiovascular

benefits might accrue with longer duration of near-normal glucose control. The ACCORD, ADVANCE, and VADT studies recruited patients who had diabetes for 8–10 years and one-third of them already had established cardiovascular disease. A large meta-analysis of multiple studies recently reported effectiveness of tight glycemic control for cardiovascular risk reduction and concluded that optimum measures to achieve this need to be established[23].

4) The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction – 1 (DIGAMI – 1) study compared "conventional" anti-diabetic therapy to intensive insulin therapy consisting of acute insulin infusion during the early hours of MI and thrice-daily subcutaneous insulin injection for the remainder of the hospital stay and a minimum of 3 months thereafter. Glucose control improved and long-term mortality decreased 30% to 50% for persons not previously receiving insulin, with decreased mortality of subsequent myocardial infarction, while the control group with type 2 diabetes had 35% to 40% overall mortality after several years. Furthermore, A1C decreased by 0.9% in the intervention group - by 1.5% among patients who had not previously received insulin. Although there was an overall reduction in adverse outcomes in patients receiving the intensive insulin regimen, it

is unclear which component (the IV insulin infusion or the intensive chronic therapy) was responsible.

5) The DIGAMI 2 study was an international (48-center) trial involving 3000 subjects with a trial design similar to that of DIGAMI 1, enrolling persons with known diabetes or with initial glucose > 11 mM/L (198 mg/dL) presenting with acute myocardial infarction with duration of symptoms < 24 hours. Study participants were randomized to 1 of 3 groups. Patients in the first group had a glucose/insulin infusion for at least 24 hours and then were treated with subcutaneous (SC) insulin. The second intervention group was treated acutely with glucose/insulin infusion for at least 24 hours and then returned to conventional treatment. The third intervention group received conventional treatment only. Sample size calculations were based on the projection that there would be 30% mortality in the control group and mortality rates of 17% and 23% in groups 1 and 2, with stratification based on cardiovascular risk and prior insulin treatment.

The study, however, was closed on May 21, 2003, because of a slow recruitment rate and only minor differences in long-term A1C between the 3 groups[28].

6) The United Kingdom Prospective Diabetes Study (UKPDS) : This multicenter study was designed to establish, in type 2 diabetic patients, whether the risk of macrovascular or microvascular complications could be reduced by intensive blood glucose control with oral hypoglycemic agents or insulin and whether any particular therapy was of advantage. A total of 3867 patients aged 25–65 years with newly diagnosed diabetes were recruited between 1977 and 1991, and studied over 10 years. The median age at baseline was 54 years; 44% were overweight (> 120% over ideal weight); and baseline HbA_{1c} was 9.1%. Therapies were randomized to include a control group on diet alone and separate groups intensively treated with either insulin or sulfonylurea (chlorpropamide, glyburide, or glipizide). Metformin was included as a randomization option in a subgroup of 342 overweight or obese patients, and much later in the study an additional subgroup of both normal-weight and overweight patients who were responding unsatisfactorily to sulfonylurea therapy were randomized to either continue on their sulfonylurea therapy alone or to have metformin combined with it.

Intensive treatment with either sulfonylureas, metformin, combinations of those two, or insulin achieved mean HbA_{1c} levels of 7%.No cardiovascular benefit and no adverse cardiovascular outcomes were noted regardless of the therapeutic agent. Hypoglycemic reactions occurred in the intensive treatment groups, but only one death from hypoglycemia was documented during 27,000 patient-years of intensive therapy.

However, the UKPDS researchers performed post-trial monitoring to determine whether there were long-term benefits of having been in the intensively treated glucose arm of the study.

The between-group differences in HbA_{1c} were lost within the first year of follow-up, but the reduced risk (24%, $P = 0.001$) of development or progression of microvascular complications in the intensively treated group persisted for 10 years. The intensively treated group also had significantly reduced risk of myocardial infarction (15%, $P = 0.01$) and death from any cause (13%, $P = 0.007$) during the follow-up period. The subgroup of overweight or obese subjects who were initially randomized to metformin therapy

showed sustained reduction in risk of myocardial infarction and death from any cause in the follow-up period.

Thus, the follow-up of the UKPDS type 2 diabetes cohort showed that the benefits of good glucose control persist even if control deteriorates at a later date.

It appears that glycemic control to levels of HbA_{1c} to 7% shows benefit in reducing total diabetes end points, including a 25% reduction in microvascular disease as compared with HbA_{1c} levels of 7.9%. This reassures those who have questioned whether the value of intensive therapy, so convincingly shown by the DCCT in type 1 diabetes, can safely be extrapolated to older patients with type 2 diabetes. It also argues against the concept of a "threshold" of glycemic control since in this group there was a benefit from this modest reduction of HbA_{1c} below 7.9% whereas in the DCCT (Diabetes Control and Complications Trial) a threshold was suggested in that further benefit was less apparent at HbA_{1c} levels below 8%.

CLINICAL OUTCOMES IN ACS:

Mortality and reinfarction rate are substantially increased in diabetic patients following myocardial infarction. In general, there is an increased mortality across the spectrum of acute coronary syndromes, with increased mortality rate at 30 days for patients with and without ST elevation (combined non-ST segment elevation infarction and unstable angina).One of the very interesting findings in the study by McGuire et al. is a grossly increased rate of reinfarction in diabetic patients without ST elevation compared to non-diabetic patients (reinfarction at 30 days 9.0 vs. 5.3%)[29].

AIM OF THE STUDY

1) To investigate the prognostic value of admission glucose and glycosylated hemoglobin levels in acute ST elevation myocardial infarction.

2) To assess the importance of long term blood glucose control as reflected by HbA1c in predicting outcome after acute ST elevation myocardial infarction.

METHODOLOGY

STUDY DESIGN:

Prospective observational study.

SOURCE OF STUDY:

Cardiology ICCU ward, Government Rajaji Hospital, Madurai.

SAMPLE SIZE :

80 patients with acute ST elevation myocardial infarction, irrespective of the diabetic status.

DURATION OF STUDY

One year (September 2010 –August 2011)

STUDY POPULATION:

INCLUSION CRITERIA:

All acute myocardial infarction patients with

- Chest pain lasting for more than 20 minutes.
- Characteristic changes of ST elevation of 1mm or more in two or more contiguous leads or new onset left bundle branch block.

- Elevated creatinine kinase MB levels >2 times the upper limit of normal.
- Age > 40 yrs.
- Both males and females.
- Presentation < 48 hrs.
- Duration of stay in the hospital > 6 hours.

EXCLUSION CRITERIA:

- Time from the onset of symptoms to hospital admission > 48 hrs.
- Patients who had received dextrose containing fluids prior to hospital admission.
- Patients receiving drugs elevating blood glucose (eg:corticosteroids).
- Post surgical or post traumatic (upto one month).
- Prior h/o MI/CAD.
- Known hypertension.
- Smokers.
- Patients with Chronic Kidney Disease /Chronic Liver Disease.
- Psychiatric patients.

STUDY END POINTS AND DEFINITIONS:

- The primary objective of the study was to estimate the incidence of complications after acute MI (congestive cardiac failure, left ventricular failure, cardiogenic shock, arrhythmias, thromboembolism, pericarditis, ventricular septal rupture, papillary muscle rupture, aneurysm) and mortality, if any during the hospital stay.

- Blood glucose is the random blood glucose measured at the time of hospital admission.

- STEMI is defined as the presence of chest pain > 20 minutes and electrocardiogram with ST elevation of >1mm in 2 or more contiguous leads or new onset LBBB with elevation of CK-MB >2 times upper limit of normal.

- Hyperglycemia was defined as a random blood sugar ≥ 200 mg/dl (American Association of Clinical Endocrinologists Guidelines - AACE 2011).

- Stress Hyperglycemia was defined as a random blood sugar ≥ 200 mg/dl (American Association of Clinical

Endocrinologists Guidelines -AACE 2011),without previous evidence of Diabetes[30].

- HbA1c levels ≥ 6.5 % was used to define diabetes in those who had no previous history of diabetes (AACE- 2011).
- HbA1c levels > 6.5 % was taken as uncontrolled diabetes in those with a previous history of diabetes (AACE – 2011).

INVESTIGATIONS :

1) Biochemical investigations

- Hemoglobin
- Random blood glucose – measured by the glucose oxidase-peroxidase method.
- Serum creatine kinase MB – measured by NAC activated method (Method of Olive Modified by Rosalki and Szasz).
- HbA1c

This was measured by ion-exchange high-performance liquid chromatography (HPLC). This method is certified by the National Glycohemoglobin Standardization Program (NGSP) as traceable to the Diabetes Control and Compliance Trial (DCCT) reference method. The

method is fully automated, thus resulting in excellent precision, with typical inter-assay variation less than 4%.

- Fasting lipid profile

2) 12 Lead electrocardiography

3) 2 -D Echocardiography

STATISTICAL ANALYSIS :

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done using **Epidemiological Information Package (EPI 2010)** developed by Centre for Disease Control, Atlanta.

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's chi square test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

Coefficient of correlation was found out using Excel software.

ETHICS:

In this study, there is no risk to the participant health, no procedure distressing to the participant was undertaken and there was no financial payment involved to the participant. A formal ethical committee approval was obtained and patients' oral, informed consent was obtained.

RESULTS

Table 1

Age distribution of subjects in the diabetic and non diabetic group

Age group	Diabetic group		Non – diabetic group	
	No	%	No	%
41 - 50 years	6	18.8	10	20.8
51 – 60 years	17	53.0	19	39.6
61 – 70 years	6	18.8	14	29.2
> 70 years	3	9.4	5	10.4
Total	32	100	48	100
Range	40 – 85 years		45 – 80 years	
Mean	58.7 years		59.4 years	
SD	9.1 years		8.8 years	

Persons aged above 40 years were included in the study. Diabetic group had an age of 58.7 $\pm$ 9.1 years and non diabetic group 59.4 $\pm$ 8.8 years. There was no significant difference in the age composition of the two groups.

Table 2

Sex distribution

Sex	Diabetic group		Non – diabetic group	
	No	**%**	**No**	**%**
Male	23	71.9	39	81.2
Female	9	28.1	9	18.8
Total	32	100	48	100

71.9% of the Diabetic and 81.2 % of the non diabetic were males. There was no statistically significant difference in the sex composition of the two groups. ($p = 0.4774$). (Graph 1)

Table 3

Killip's class at admission of diabetic and non diabetic subjects

Killip class	Diabetic group		Non – diabetic group	
	No	%	No	%
I	23	71.9	34	70.9
II	5	15.5	5	10.4
III	2	6.25	5	10.4
IV	2	6.25	4	8.3
Total	32	100	48	100

Majority of cases included in both the Groups (71.9% and 70.9%) had a Killip score of I (Graph 2).

Table 4

Admission blood sugar of diabetics and non diabetics

Blood sugar (mg / dl)	Diabetic group		Non – diabetic group	
	No	%	No	%
(≤200mg/dl)	15	46.9	43	89.6
(>200mg/dl)	17	53.1	5	10.4
Range	66 – 474		58 – 355	
Mean	229.8		131.3	
SD	107.9		67.0	
'p'	**0.0001 Significant**			

Mean blood sugar of the diabetic group was 229.8 mg/dl and the non diabetic group was 131.3 mg/dl. This difference was statistically significant (Graph 3).

Table 5

Lipid profile of diabetic and non diabetic subjects

Lipid	Diabetic group		Non-diabetic group		'p'
	Mean	**SD**	**Mean**	**SD**	
Total Cholesterol	194.7	39.4	174.3	29.8	**0.0021 Significant**
TGL	195.6	35.7	173.3	29.8	**0.0004 Significant**
LDL	114.2	37.0	90.7	33.4	**0.002 Significant**
HDL	48.2	8.8	44.4	8.8	**0.0426 Significant**
VLDL	39.8	4.8	42.0	6.0	0.306 Not Significant

Mean Lipid values of the diabetic group (except VLDL) were significantly different than that of the non diabetic group.

Table 6

Relationship between blood sugar values and LVEF

Blood sugar	Diabetic cases				Non-diabetic cases			
	LVEF ≥ 40%		**LVEF < 40%**		**LVEF ≥ 40%**		**LVEF < 40%**	
	No.	%	No.	%	No.	%	No.	%
Controlled (< 200mg/dl)	13	86.7	2	13.3	31	74.4	12	25.6
Not controlled (≥ 200 mg./dl)	1	5.9	16	94.1	1	20	4	80
'P'	**0.0001 Significant**				**0.0366 Significant**			
'r' Coefficient of correlation	**-0.7153**				**-0.5124**			

There exists significant negative correlation between blood sugar values and LVEF values in both the groups.

Table 7

Relationship between HbA1C values and LVEF %

HbA1C	Diabetic group		Non-diabetic group	
	LVEF		LVEF	
	Normal (> 40%)	Abnormal (≤ 40%)	Normal (> 40%)	Abnormal (≤ 40%)
	No	No	No	No
≤ 6.5 %	5	-	32	5
>6.5 %	9	18	11	-
P	0.0171 Significant		0.0099 Significant	
'r' Coefficient of correlation	-0.6345		-0.5149	

There exists significant negative correlation between HbA1C values and LVEF values in both the groups.

Table 8 : Left ventricular ejection fraction

Groups	L V E F %				
	Normal		Abnormal		Mean / SD
	No.	%	No.	%	
A) **Group 1** (Uncontrolled Diabetes)(27)	9	33.3	18	66.7	39.9 ± 10.2
B)**Group 2** (Controlled Diabetes)(5)	5	100	-	-	49.8 ± 5.9
C) **Group 3** (Stress Hyperglycemia)(2)	-	-	2	100	35.5 ± 2.1
D)**Group 4** (Undiagnosed Diabetes)(9)	-	-	9	100	33.1 ± 3
E) **Group 5** (Normal cases) (37)	32	86.5	5	13.5	54.9 ± 12.5
'p'	**0.0001 Significant**				

Subjects with undiagnosed diabetes, stress hyperglycemia and uncontrolled diabetes had lower left ventricular injection fraction in that order compared to the controlled diabetics and the non diabetic subjects (Graph 5).

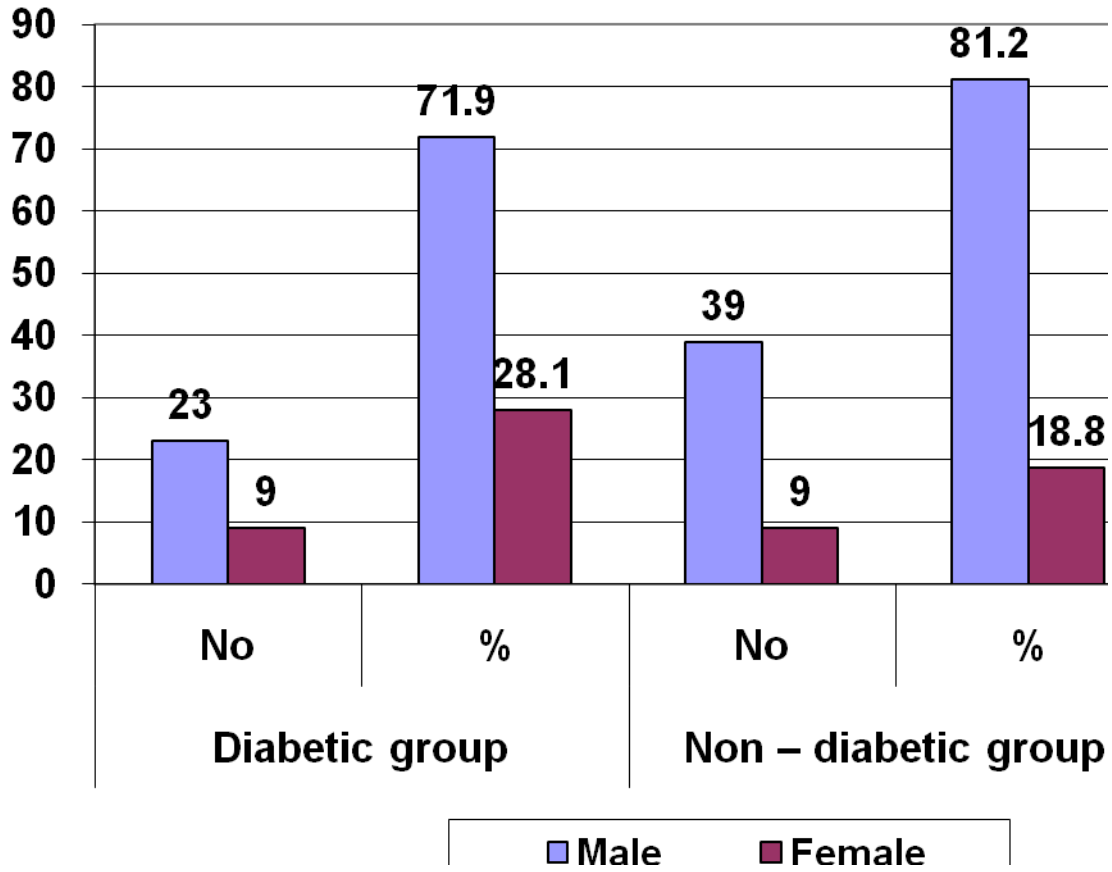
Table 9

Incidence of complications

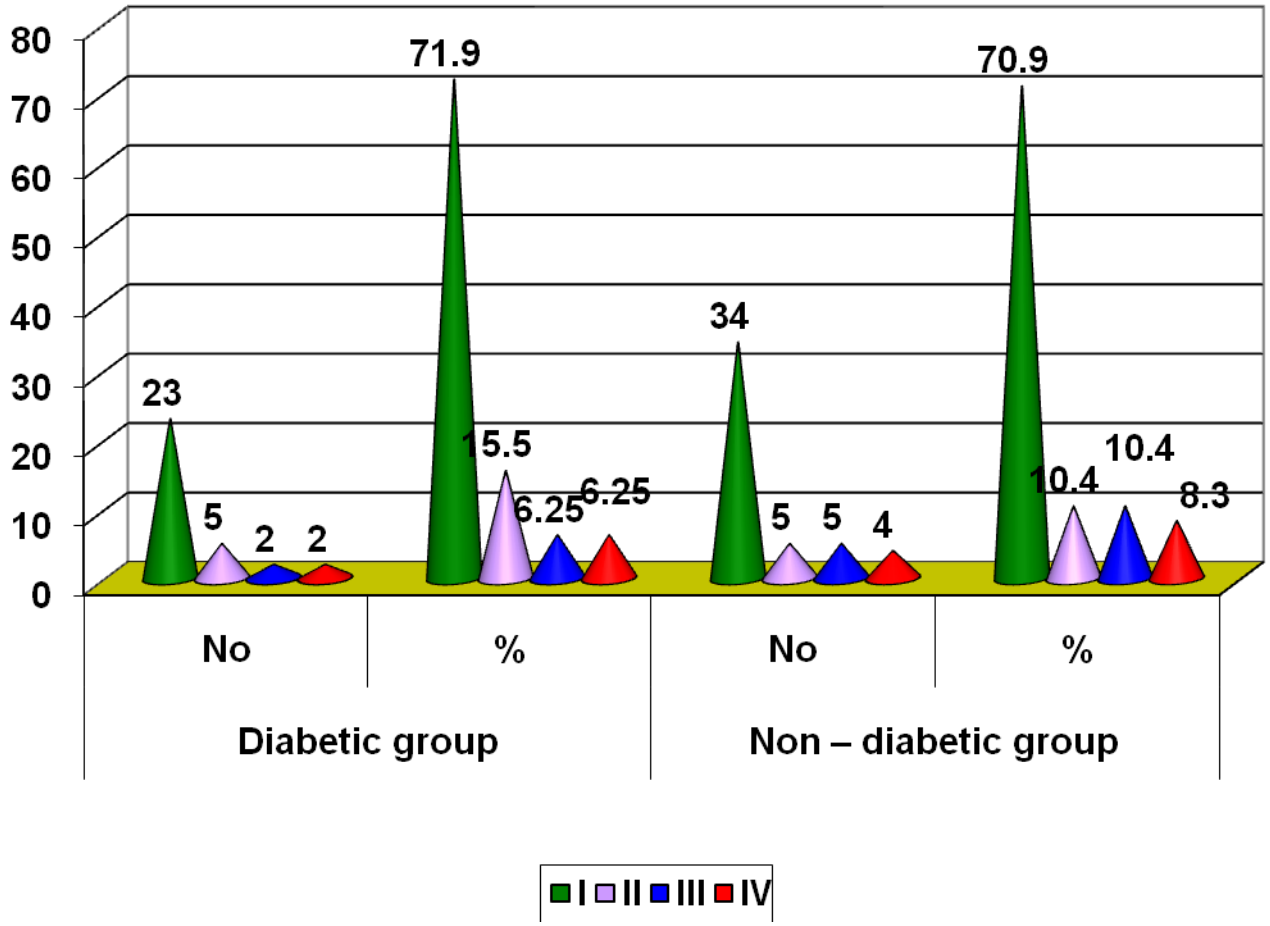
Groups	Complications			
	Present		Absent	
	No	%	No	%
A) **Group1** (Uncontrolled Diabetes) (27)	19	70.4	8	29.6
B) **Group 2** (Controlled Diabetes) (5)	1	20	4	80
C)**Group 3** (Stress Hyperglycemia) (2)	2	100	-	-
D) **Group 4** (Undiagnosed Diabetes) (9)	6	66.7	3	33.3
E)**Group 5** (Normal cases) (37)	3	8.1	34	91.9

The incidence of complications were found to be higher in subjects with stress hyperglycemia, uncontrolled diabetes and undiagnosed diabetes in that order (Graph 6).

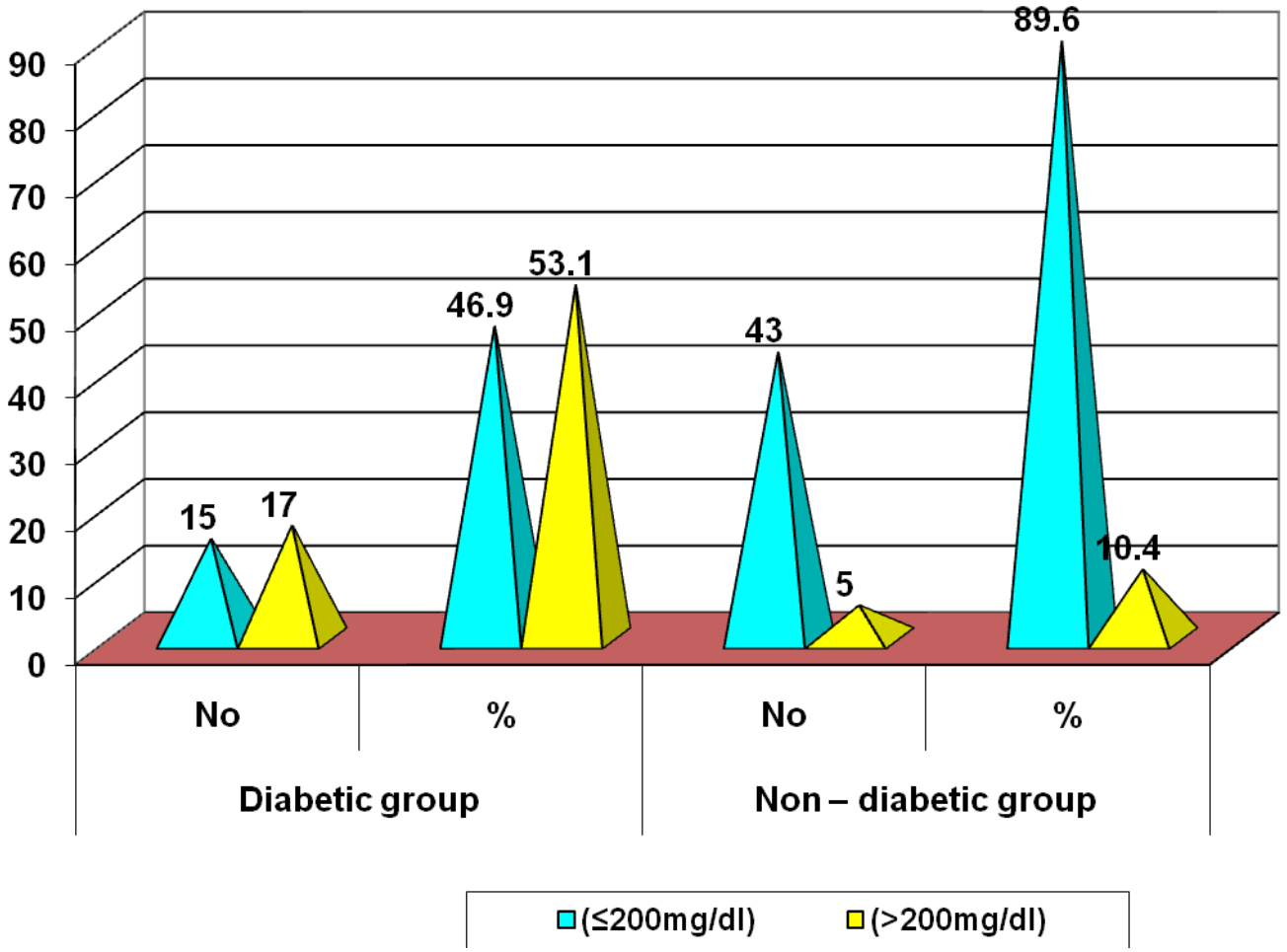
Graph 1: SEX DISTRIBUTION



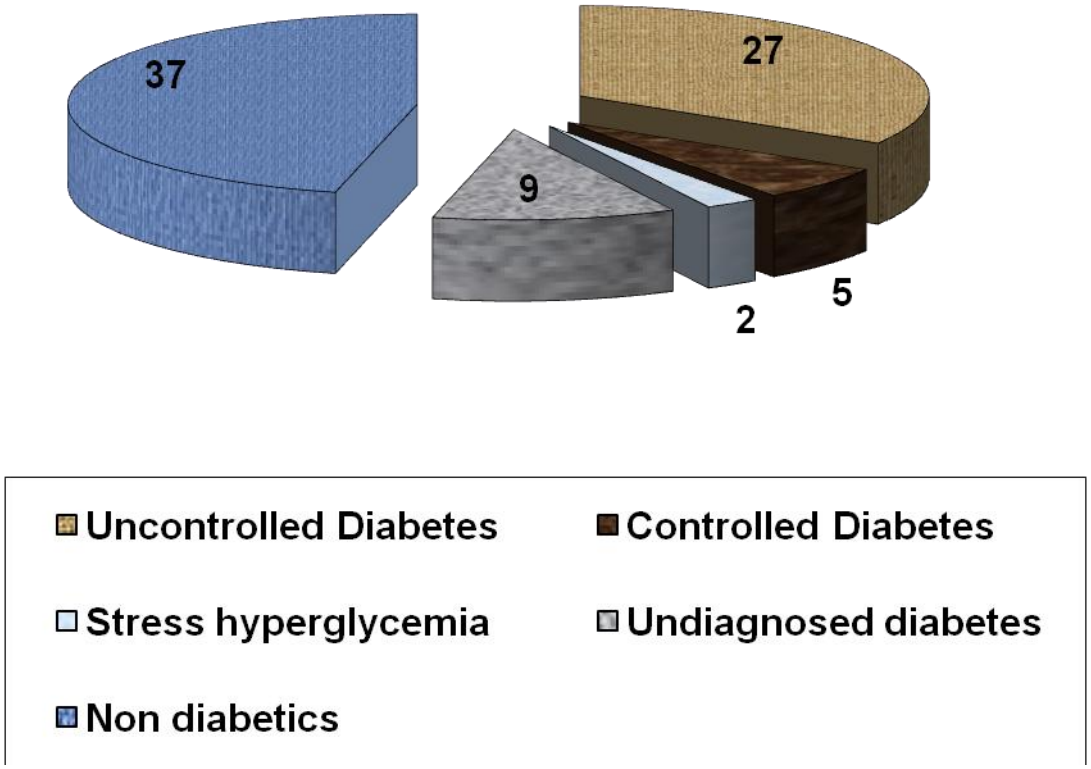
Graph 2: Killip's class at admission of diabetic and non diabetic subjects



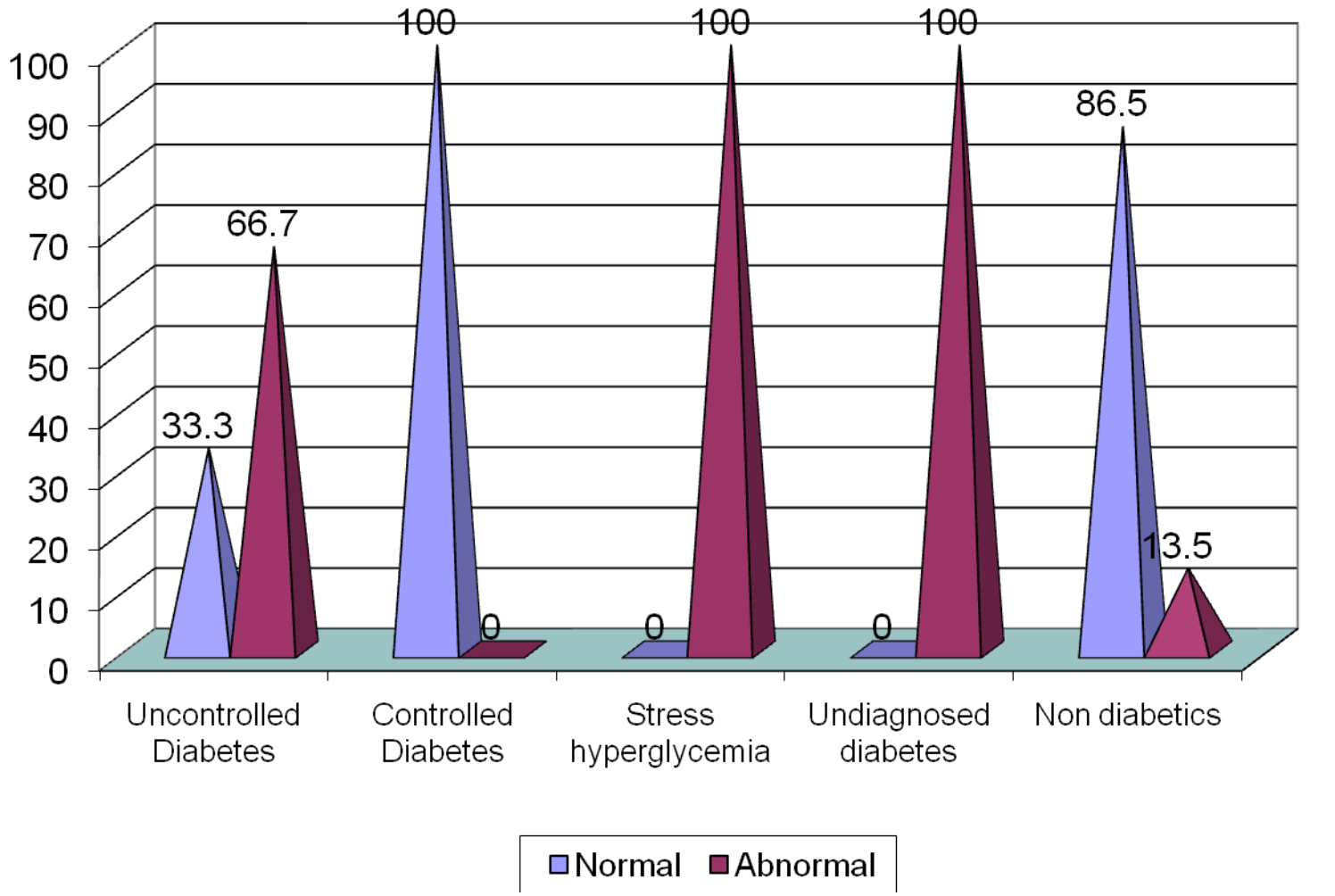
Graph 3: ADMISSION BLOOD SUGAR OF DIABETICS AND NON DIABETICS



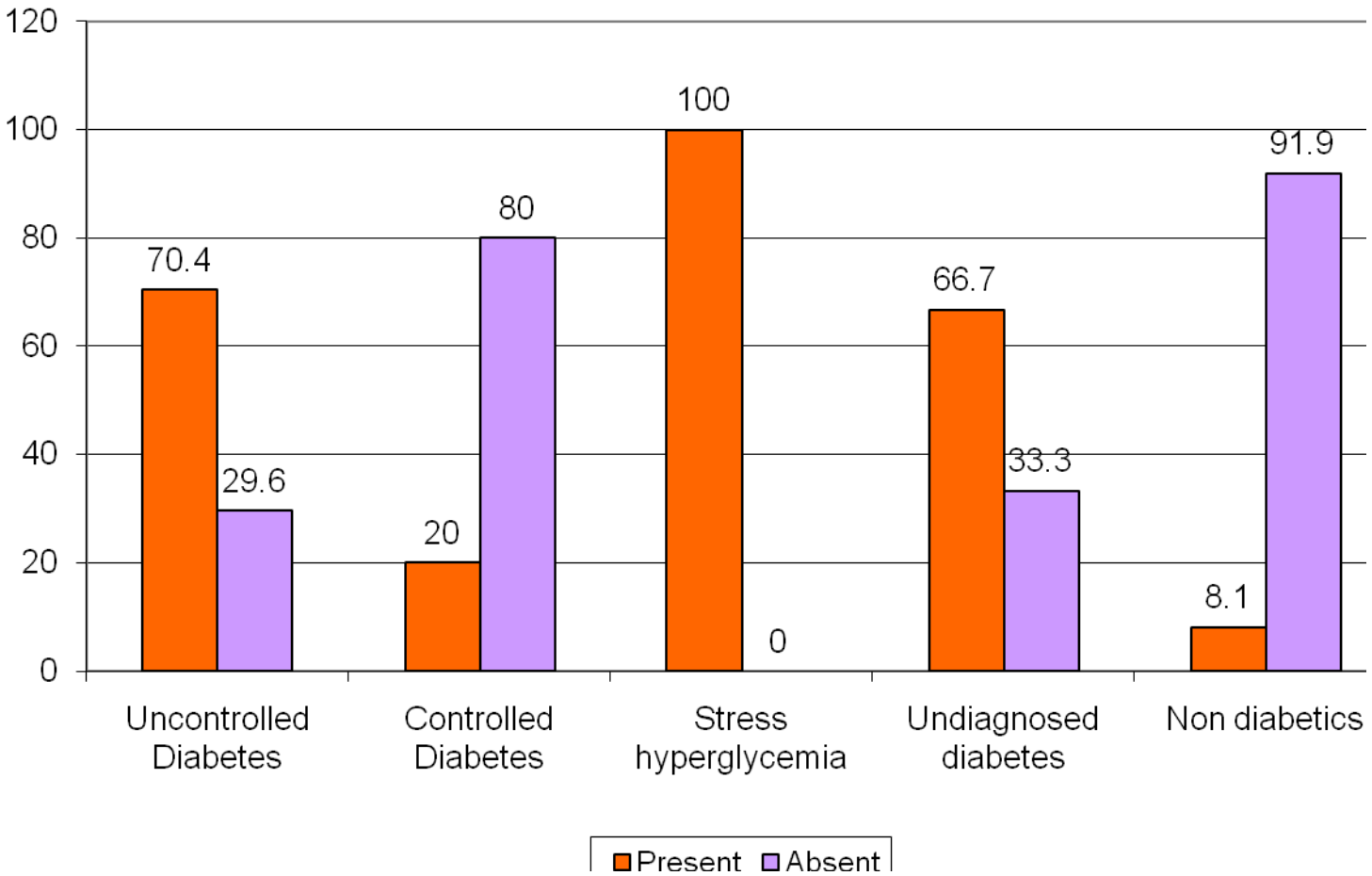
Graph 4: Distribution of cases according to diabetic status



Graph 5: Left ventricular ejection fraction in the different groups



Graph 6: Incidence of complications in the different groups



DISCUSSION

In our study, we included 80 cases of myocardial infarction, who had presented within 48 hours of onset of symptoms, irrespective of diabetic status and who satisfied the inclusion criteria. The patient's history was taken and physical examination findings were noted. At admission, patient's blood glucose values, electrocardiogram, cardiac enzymes and HbA1c were done. Fasting lipid profile and echocardiography were done during hospital stay. The patients were followed up during the hospital stay and in-hospital complications were noted.

A comparative analysis of those with a previous history of diabetes and those without, was done initially. The diabetic group had an age distribution of 58.7±9.1 years and the non diabetic group 59.4±8.8 years. 71.9 % of the diabetics and 81.2 % of the non diabetics were males. There was no significant difference in the age or sex composition between the groups. Majority of cases included in both groups(71.9 % of diabetics and 79.8 % of non diabetics) had a Killip's score of I. The mean blood sugar of the diabetic group was 229.8 mg/dl and the non diabetic group was 131.3 mg/dl. The difference was statistically significant.

The mean HbA1c of the diabetic group was 9.8 % and that of the non diabetic group was 6.57 %.This difference was statistically different. This is in accordance with a study by Tenerz et al that showed that patients with a history of diabetes, had higher mean hemoglobin A1c values than those with newly diagnosed diabetes, and patients with newly diagnosed diabetes had higher mean hemoglobin A1c values than those without diabetes[30].The diabetics were also found to have more deranged lipid levels as compared to the non diabetics.

The 80 patients included in this study were further stratified into five groups,based on previous history of diabetes, blood glucose levels at admission and HbA1c levels (American Association of Clinical Endocrinologists Guidelines 2011).

Group 1 (uncontrolled diabetes)
Previous history of diabetes with HbA1c > 6.5 %.

Group 2 (controlled diabetes)
Previous history of diabetes with HbA1c ≤ 6.5 %.

Group 3 (Stress hyperglycemia) :
No previous history of diabetes, random blood glucose at admission ≥ 200 mg/dl and HbA1c<6.5 %.

Group 4 (Undiagnosed diabetes)
No previous history of diabetes,random blood glucose ≥ 200 mg/dl and HbA1c ≥ 6.5%.

Group 5 (Non diabetic)
No previous history of diabetes,random blood glucose < 200 mg/dl and HbA1c < 6.5 %.

There were 27 subjects under group 1 (uncontrolled diabetes) of which 70.4 % had complications during hospital stay and 66.7 % had an LVEF ≤ 40 %.

Among the 5 patients in group 2 (controlled diabetes), only 1 developed complication during hospital stay and all had an LVEF >40%.

In group 3 (stress hyperglycemia),both patients developed complications and had an LVEF ≤ 40 %.

There were 9 subjects in group 4 (undiagnosed diabetes),out of which 66.7 % developed complications and all had an LVEF ≤ 40 %.

Group 5 included 37 patients, out of which only 8.1 % developed complications and only 13.5 % had an LVEF ≤ 40 %.

It was noted from this study that the in hospital complication rate was higher in the uncontrolled diabetes group ,the newly diagnosed diabetic group and the stress hyperglycemia group. This is in concordance with the study by Nazneem et al.,which showed that patients known to have diabetes and those with hyperglycemia without a history of diabetes had a worse outcome after myocardial infarction[8].This may be attributed to the fact that those patients with no

prior history of diabetes had the lowest rates of exposure to cardiovascular disease modifying drugs like aspirin, statins, angiotensin converting enzyme inhibitors and beta blockers.

Our study showed that those with uncontrolled diabetes and the newly diagnosed diabetics, who had a higher incidence of complications had higher HbA1c levels and higher admission blood glucose values. These two groups also had lower left ventricular ejection fractions. The contribution of stress hyperglycemia in these groups cannot be determined because previous records of blood glucose levels were not available.

While hyperglycemia is a marker of post AMI stress, insulin resistance is related to the intensity of the stress. A chronic pre-existing abnormal glycometabolic state inevitably affects the degree of metabolic response to stress, hence higher blood glucose levels are found during stress in patients with previously known IGT[31]. This could explain the occurrence of high blood glucose levels and also higher HbA1c levels in this subset of patients. A study done by Mahmut et al. have shown similar results that both acute and chronic glycometabolic states are an indicator of prognosis after AMI.

The stress hyperglycemia group had lower left ventricular ejection fraction and increased incidence of complications compared to the non diabetic subjects.

Several hypothesis have been put forward to explain the relation between stress hyperglycemia and poor outcome. Stress hyperglycemia may be a marker of extensive myocardial damage, reflecting a surge of stress hormones such as catecholamines and cortisol that produce or augment an insulin resistant state.[32,33.] Relative insulin deficiency and excess catecholamines reduce glucose uptake by the ischemic myocardium and promote lipolysis and increased circulating free fatty acids. The latter inhibit glucose oxidation (the "glucose-fatty cid cycle") and are toxic to ischemic myocardium, resulting in increased membrane damage, arrhythmias, and reduced contractility. [34,35,36,37].

Alternatively, elevated blood glucose levels per se adversely affect outcome through the cumulative effects of several mechanisms, including induction of endothelial dysfunction[38], oxidative stress[39], hypercoagulability, and impaired fibrinolysis[40]. Admission hyperglycemia may not only be the cause of more severe myocardial damage but also its consequence. Large infarcts are more likely to cause catecholamine release, which affect acid and glucose homeostasis.

But conclusions on the effect of stress hyperglycemia on prognosis after myocardial infarction cannot be drawn in our study because of the relatively small number of patients in this group.

However, the results of our study clearly show that long term blood glucose control, as reflected by the HbA1c levels, have an important role in predicting the prognosis after acute ST elevation MI. Many of the studies examining acute MI patients in the hyperglycemic state did not measure HbA1c, and hence, they were not able to demonstrate pre-existing diabetes. Undiagnosed diabetes was found in 4.3% of patients in one study, contributing to approximately 10% of mortality[41]. Levetan et al[42] also demonstrated that one-third of hospitalized patients had at least one glucose level reading higher than 200 mg/dl. In the presence of high glucose levels, stress hyperglycemia should be differentiated from diabetes. The admission glucose level can not be used to predict the prognosis in diabetic patients. Because admission blood glucose levels had begun to lose its significance in predicting the prognosis of patients with acute MI in diabetics, recently focus has been on HbA1c level as a prognostic marker in these patients.

Therefore, HbA1c can be used as a tool in these settings to identify patients with pre existing diabetes and to differentiate between uncontrolled diabetes and stress hyperglycemia and also assess prognosis in these separate subsets of patients.

LIMITATIONS OF THE STUDY

1) Our study included only a limited number of patients and there was an unequal distribution of cases among the different groups as HbA1c could not be done as a routine investigation in all patients with acute MI in our hospital.
2) The diagnosis of pre existing diabetes could not be confirmed by the oral glucose tolerance test after discharge from hospital.
3) Mortality and complication rates are also influenced by factors such as the presence or absence of recanalization, infarct sites, the time from disease onset to treatment, Killip's classification at admission, ST segment elevation resolution and left ventricular function.
4) Since we included only those patients who survived the first 6 hours of hospital stay for feasibility of acquiring the necessary investigations ,the actual mortality rates cannot be established by our study.
5) Despite these limitations,our results clearly demonstrated that both acute and chronic glycometabolic states are indicators of prognosis after acute MI.

CONCLUSIONS

The following conclusions were made after the completion of the study:

- Subjects with uncontrolled diabetes had a higher incidence of complications during hospital stay and a lower left ventricular ejection fraction.

- Subjects with newly diagnosed diabetes had higher admission blood glucose levels and HbA1c which correlated with a higher incidence of complications during hospital stay and a lower left ventricular ejection fraction.

- There was a significant negative correlation between HbA1c levels and left ventricular ejection fraction.

- There was a significant negative correlation between admission blood glucose levels and left ventricular ejection fraction.

- Our results suggest that both acute and chronic hyperglycemia are independent predictors of adverse outcome after acute ST elevation myocardial infarction. Hence, measurement of both blood glucose as well as HbA1c enables identification of these high risk groups for aggressive management.

SUMMARY

A prospective, observational study was conducted in 80 patients with acute ST elevation myocardial infarction, irrespective of their diabetic status, in Government Rajaji Hospital, Madurai for a period of one year. The aim of the study was to investigate the prognostic importance of admission blood glucose and glycosylated hemoglobin levels in patients with acute ST elevation myocardial infarction. The results showed that the in hospital complication rate was higher in the uncontrolled diabetes group ,the newly diagnosed diabetic group and the stress hyperglycemia group.

Our study showed that those with uncontrolled diabetes and the newly diagnosed diabetics, who had a higher incidence of complications had higher HbA1c levels and higher admission blood glucose values. These two groups also had lower left ventricular ejection fractions. The stress hyperglycemia group had lower left ventricular ejection fraction and increased incidence of complications compared to the non diabetic subjects. There was a significant negative correlation between HbA1c levels and left ventricular ejection fraction. There was a significant negative correlation between admission blood glucose levels and left ventricular ejection fraction. Our results suggest that both acute and

chronic hyperglycemia are independent predictors of adverse outcome after acute ST elevation myocardial infarction. Hence, measurement of both blood glucose as well as HbA1c enables identification of these high risk groups for aggressive management

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PROFORMA

Name: Age: Sex:

Date of admission:

Date of discharge:

Past history:

- Diabetes
- Hypertension
- Ischaemic heart disease
- Surgery

Personal history:

- Smoking (if yes,no. of pack yrs.)
- Tobacco use

Killip's Class :

INVESTIGATIONS:

- Admission Blood Glucose
- Creatine kinase MB
- Lipid Profile
  Total cholesterol -

  Triglycerides -

  LDL -

  VLDL -

  HDL -
- HbA1c

- Electrocardiography

  Rate Rhythm QRS axis PR interval

  QRS interval QTc interval

  ST elevation

  T wave changes

  Pathological Q waves

  Interpretation

- Echocardiography
  Regional wall motion abnormality

  LVEF

  Diastolic dysfunction

  Mitral regurgitation

  Clot / aneurysm

  Pericardial effusion

Thrombolysis – done / not done

In hospital complications:

- CCF/LVF
- Cardiogenic shock
- Arrhythmias
- Thromboembolism
- Pericarditis
- Rupture of interventricular septum
- Rupture of papillary muscle
- Aneurysm
- Any other

Follow up upto date of discharge .

MASTER CHART

No	Name	Age	Sex	Type of diab.	diabetes	killip class	blood sugar	TC	TGL	LDL	HDL	VLDL	Hba1c	LVEF	Thrombolysis / Complications
1	tamilselvi	46	f	E	No	III	104	190	186	103	41	44	6.3%	55	t
2	sukumar	65	m	E	No	III	87	178	192	78	44	38	6.3%	57	t
3	ganapathy	65	m	E	No	II	63	162	184	92	42	40	5.7%	71	t
4	samuel	48	m	E	No	I	63	186	190	76	38	38	5.0%	72	t
5	subbulakshmi	55	f	E	No	I	151	188	174	78	42	40	6.3%	52	t
6	sonai	50	m	D	No	II	203	215	229	50	45	40	7.6%	38	grII MR / t
7	murugesan	47	m	E	No	I	162	209	216	71	44	46	5.3%	54	t
8	mohammed	57	m	E	No	I	58	155	138	98	27	40	5.2%	58	t
9	ramar	70	m	B	Yes	III	146	187	108	127	22	38	5.6%	45	t
10	mayandi	50	m	E	No	I	103	178	168	103	33	42	5.8%	44	nt
11	rathinam	70	m	D	No	IV	203	216	174	98	46	32	14.2%	32	t
12	mahadevan	52	m	A	Yes	I	202	339	210	255	42	42	10.3%	38	t
13	satasivam	76	m	E	No	I	128	221	148	190	40	42	6.4%	35	t
14	radhakrishnan	48	m	A	Yes	I	320	205	224	174	38	41	9.6%	31	large lv clot / nt / chb
15	manoharan	50	m	E	No	I	130	162	171	105	45	38	5.8%	45	t
16	karungan	58	m	E	No	I	83	174	162	128	40	40	6.4%	51	nt
17	sonai	57	m	E	No	III	171	118	170	42	34	42	6.3%	42	MR grI / nt
18	balusamy	60	m	D	No	II	201	120	150	54	30	42	8.5%	31	large lv clot / t
19	kannan	56	m	D	No	I	255	181	121	117	24	40	9.8%	34	large lv clot / nt / chb
20	soundaravalli	60	f	A	Yes	I	285	211	148	106	38	37	8.8%	50	t
21	jeyaraman	56	m	A	Yes	I	232	198	130	108	44	40	10.9%	40	ar I / nt / 1st block

22	vadivel	56	m	A	Yes	I	379	208	217	87	42	39	8.5%	47	lv apical clot / t
23	murugesan	52	m	E	No	I	90	179	182	91	36	40	6.0%	49	t
24	palaniammal	69	f	A	Yes	II	274	205	176	88	42	45	8.5%	35	t
25	anjagnanam	55	m	E	No	I	149	196	180	74	44	48	6.2%	61	t
26	kalaiselvan	56	m	E	No	II	104	178	182	80	44	46	6.3%	30	large lv clot / t
27	devadoss	53	m	E	No	I	87	180	174	89	46	40	6.4%	53	vt / nt
28	karupaiah	67	m	D	No	I	204	184	176	93	44	46	6.7%	32	MR I / t
29	asiya	55	f	E	No	I	82	188	180	89	40	46	6.2%	52	MR I / t
30	ayyam perumal	57	m	E	No	I	87	178	176	77	43	48	6.5%	55	t
31	gopal	65	m	A	Yes	I	286	187	180	120	50	42	12.8%	38	MR II /t
32	narayanan	62	m	E	No	I	120	165	168	112	45	46	6.0%	41	t
33	balakrishnan	45	m	E	No	I	130	229	260	138	52	39	5.8%	69	t
34	gurusamy	65	m	B	Yes	II	191	203	224	143	56	39	5.9%	54	t
35	karuppaiah	60	m	D	No	I	208	165	240	39	58	68	6.7%	31	t
36	sahul ahmed	74	m	A	Yes	I	309	122	220	73	44	35	8.2%	30	MR,LV apical clot / t/CCF/cpa(rec)
37	chinnaiya	68	m	E	No	I	171	154	187	77	45	48	5.8%	65	MR I / t
38	velammal	45	f	A	Yes	I	341	224	225	134	49	41	14.7%	27	MR I / transient CHB / t
39	rakkaiyee	70	f	E	No	I	121	167	174	67	46	39	6.3%	62	nt
40	chinnaponnu	55	f	A	Yes	I	207	215	189	86	46	42	6.6%	52	t
41	palsamy	61	m	E	No	II	126	198	167	92	48	42	5.4%	67	t
42	shanmuganathan	57	m	A	Yes	I	474	227	254	132	52	41	13.9%	33	grII MR / t

43	valliamal	60	f	A	Yes	I	431	161	249	71	49	41	11.7%	31	MR,LV apical clot / t/CCF/cpa(rec)
44	iyavu	75	m	E	No	IV	118	136	185	58	37	41	6.4%	33	CHB,HIE / t
45	karupayee	65	f	C	No	I	210	187	197	79	52	46	6.0%	37	CHB / nt
46	muthusamy	60	m	A	Yes	II	231	237	201	150	40	42	10.1%	35	large lv clot / nt / chb
47	gajendran	55	m	A	Yes	I	385	221	207	137	41	43	10.0%	47	vt / nt
48	ramkumar	45	m	C	No	I	205	187	165	156	54	48	5.5%	34	trivial mr/ar / nt / vt/c shock
49	rakamal	55	f	A	Yes	IV	259	202	280	104	56	42	13.5%	41	MR,LV apical clot / t/CCF/cpa(rec)
50	madurasamy	72	m	D	No	I	226	132	181	60	36	36	14.2%	30	MR III / nt
51	sathyamurthy	73	m	A	Yes	I	225	177	168	76	49	45	6.7%	73	t
52	dhanam	55	f	E	No	I	90	250	179	173	36	41	6.1%	42	MR I /t
53	sevugan	46	m	A	Yes	I	322	212	206	98	56	43	11.6%	28	grII MR / t
54	balu	48	m	A	Yes	I	301	199	187	131	45	46	13.1%	35	grII MR /t
55	ganesan	58	m	A	Yes	I	402	187	185	92	56	44	11.9%	38	grI MR,severe LV / t/death(cpa)
56	kumaran	49	m	A	Yes	IV	389	188	176	89	54	40	10.6%	44	CHB / nt
57	durai	58	m	A	Yes	I	305	196	190	90	56	44	13.3%	36	grII MR / t
58	mariammal	56	f	A	Yes	I	209	187	192	78	55	41	8.9%	36	MR,LV apical clot / t/CCF/cpa(rec)
59	iyapan	56	m	E	No	i	66	167	145	82	50	44	6.4%	40	t
60	ramamoorthy	47	m	E	No	I	60	157	160	67	45	40	6.5%	34	large lv clot / t
61	subbaiah	74	m	D	No	I	206	167	154	87	56	48	6.9%	38	trivial mr/ar / t
62	joseph selvaraj	54	m	A	Yes	I	366	189	198	135	48	40	8.9%	59	t
63	pitchai	47	m	B	Yes	I	87	198	201	143	62	42	6.1%	50	t
64	thirumal	58	m	E	No	III	69	160	146	88	45	40	5.8%	76	t
65	santhanalakshmi	66	f	E	No	I	84	178	180	114	56	48	5.7%	65	grI MR / t
66	muthulakshmi	60	f	E	No	IV	121	190	186	146	60	43	5.2%	74	nt

67	periyakaruppan	65	m	E	No	I	136	114	120	74	44	42	5.9%	63	t/transient CHB
68	gopal	68	m	E	No	IV	166	150	222	44	76	40	5.4%	72	vt / nt
69	karupasamy	65	m	E	No	I	99	153	136	72	46	40	6.4%	53	t
70	irudayasamy	68	m	B	Yes	I	96	189	199	113	59	40	6.1%	57	t
71	subramany	85	m	A	Yes	II	251	167	189	121	62	43	7.0%	45	T
72	iyyamal	64	f	A	Yes	I	271	111	225	67	45	26	11.7%	31	MRI / transient CHB / t
73	velandi	50	m	D	No	I	201	144	198	64	54	48	7.0%	32	trivial mr/ar / t
74	vallavan	65	m	E	No	I	119	138	174	64	49	35	5.9%	60	t
75	ramu	55	m	E	No	I	92	126	110	69	42	32	5.5%	71	t
76	meenal	60	m	E	No	I	63	227	124	160	42	34	6.2%	53	t
77	kathiravan	51	m	B	Yes	II	137	170	128	102	42	26	6.3%	43	grII MR,LV apical clot / recurrent vt / nt
78	pushpam	80	f	E	No	III	126	190	136	94	45	28	6.4%	54	t
79	shanmugam	60	m	A	Yes	I	326	117	195	132	40	33	8.4%	38	MR I / transient CHB / t
80	meenakshi	60	f	A	Yes	III	315	192	177	92	62	32	13.4%	35	death (cra) / t

t - Thrombolysed nt - not thrombolysed LV Clot - Left ventricular clot

CCF - Congestive cardiac failure CHB - Complete heart block MR - Mitral Regurgitation

HIE - Hypoxic Ischemic Encephalopathy AR - Aortic Regurgitation CPA - Cardio Pulmonary

VT - Ventricular Tachycardia LVF - Left ventricular failure Arrest

A Uncontrolled Diabetes

B Controlled Diabetes

C Stress hyperglycemia

D Undiagnosed Diabetes

E Non Diabetic